UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,620	10/03/2003	Stephen J. Reinl	34150/0008	8138

27860 7590 06/08/2006

LARGE SCALE BIOLOGY CORPORATION
3333 VACA VALLEY PARKWAY
SUITE 1000
VACAVILLE, CA 95688

EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 06/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	**Application No.** 10/679,620	**Applicant(s)** REINL ET AL.
	Examiner Lynn Bristol	**Art Unit** 1643

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-14 and 18-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
   Paper No(s)/Mail Date *11/22/04; 1/27/05;* 4/18/2005 LAB
4) ☐ Interview Summary (PTO-413)
   Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. Claims 1-26 are all the pending claims for this application.

2. The two Preliminary Amendments filed on August 13 and 16, 2004 each request correction of the date of filing from October 3, 2003 to October 3, 2002 for the corresponding U.S. provisional application, 60/415,940, as cross-referenced in the specification. The amendment to the specification is noted and entered.

Election/Restrictions

3. Applicant's election of in the reply filed on May 4, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 15-17 are all the claims under examination with claims 1-13 and 18-26 withdrawn as being directed to non-elected subject matter.

Information Disclosure Statement

4. The US patent references and the non-patent literature references cited in the IDSs of November 22, 2004, January 27, 2005, and April 18, 2005 have been considered and made of record.

Sequence Compliance

5. Pursuant to 37 CFR 1.821, a sequence identifier must be provided for any amino acid sequences of four or more residues or nucleotide sequences of 10 or more nucleotides. The following omission has been identified in the specification:

p. 59, [¶220]- EQKLISEEDL

Applicants will need to provide a revised Sequence Listing, a computer readable form of the Sequence Listing and a statement. Please see the attached Notice to Comply Form, for which the Examiner has set a 3-month shortened statutory period for response.

Specification

6. Applicants will need to amend the specification by providing a sequence identifier for the following sequence in addition to any other sequences that may not be properly identified:

p. 59, [220]- EQKLISEEDL

Applicants will need to provide a revised Sequence Listing, a computer readable form of the Sequence Listing and a statement. Please see the attached Notice to Comply Form, for which the Examiner has set a 3-month shortened statutory period for response.

7. The use of several trademarks (e.g., Geneware™, Sepharose®) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

8. The specification is objected to for the "Conclusions" section (pp. 129-145), which appears to set forth a claim set in addition to the claim set appearing on pp. 147-152. Amending the specification to delete pages 129-143 would overcome this objection.

9. The deposit information for plasmid DNAs in [¶456] at lines 7-9 has been omitted from the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 15-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claim 15 is indefinite, more especially for the recitation in step (d)(iii) as it is unclear where and under what conditions the preproprotein can be processed into the mature polypeptide. Is it intended that only the host cell initiate this maturation step(s) or can one of skill in the art obtain the preproprotein from the host cell or cultured medium, and cleave the pre- and pro- regions chemically to obtain the mature forms of the first and second proteins of interest?

b) Claim 16 is indefinite for the recitation "bond to form a mature multimeric protein" as it is unclear whether the two copies of the mature polypeptide are intended to bind to each other, or to other polypeptides. In other words, should the mature "first protein of interest" bond to the mature "second protein of interest", or only to each of their corresponding proteins? Alternatively, should the two mature proteins bond to any other polypeptides?

c) Claim 17 is indefinite for the recitation "a derivative of either the antibody or the Fab fragment" as it is unclear what Applicants intended derivation(s) of either the antibody or Fab fragment should be. Do these include amino acid substitutions, insertions, deletions, etc., and to what part of the structure of the molecule should any changes be made? Alternatively, "a derivative" could encompass antibody- or Fab fragment-conjugates to proteins and non-proteins alike, or chimeric and humanized antibodies/Fab fragments.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claim 15 is rejected under 35 U.S.C. 102(a) as being anticipated by Francois et al. (Plant Physiology 128:1346-1358 (April 2002); hereinafter referred to as "Francois").

Claim 15 is directed to a method for making a multimeric protein comprising expressing in a transfected host cell an artificial polynucleotide encoding in the following order and being operatively linked: a signal peptide sequence, a first peptide of interest, a propeptide and a second peptide of interest, where the first and second peptides of interest are the same or different, and where the expressed product is a preproprotein which is then processed into a mature polypeptide.

Francois discloses a natural polyprotein, *Impatiens balsamia* antimicrobial protein (IbAMP), occurring in seeds of plants, that consists of a leader peptide followed by six 20-amino acid long mature peptide domains, each flanked at either side by cleavable propeptide domains ranging from 16-35 amino acids in length. Francois discloses methods for delivering different AMPs in Arabidopsis using plant transformation vector constructs shown in Figure 1 and comprising the following artificial polynucleotide sequence: a leader peptide (encoding 28 amino acids from DmAMP1 precursor), DmAMP1 (encoding 50 amino acids or mature protein), cleavable propeptide (encoding fifth propeptide from IbAMP), and RsAFP2 (encoding 51 amino acids or mature protein). DmAMP1 and RsAFP2 belong to the family of plant defensins. The chimeric polyprotein was found to be expressed (Table 1 comparing expression of chimeric polyprotein from the pFAJ3105 construct) and cleaved (Figure 5 shows chromatographic purification of DmAMP1 and RsAFP2 proteins from plant extracts) in transgenic Arabidopsis plant leaves and the individual AMPs were secreted into the extracellular space (p. 1349, Col. 2, ¶2) where they were found to exert antifungal activity (table IV). Applicant is reminded that because the claim recites “comprising” language, artificial polynucleotides encoding any "peptide of interest" is encompassed within the scope, and is thus anticipated by Francois.

13. Claims 15-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Wu et al. (Protein Engineering 14(12):1025-1033 (December 2001); hereinafter referred to as "Wu").

The interpretation of Claim 15 is discussed supra. Claim 16 is drawn to two copies of the mature polypeptide bonding to form a mature multimeric protein, and Claim 17 is drawn the multimeric protein being a derivative of an antibody or Fab fragment.

Wu discloses a single chain chimeric anti-CD20 antibody encompassing an scFv assembled VL-linker-VH and the human IgG1 hinge and Fc regions (scFv-Fc). Wu discloses methods for cloning and delivering an expression vector to host cells (p. 1026, Col. 2, ¶3-4) for expression of an artificial polynucleotide (p. 1026, Col. 1, ¶3- Col. 2, ¶2; Figure 1A and 1B) encoding in the order of a signal peptide from a murine kappa light chain (p. 1026, Col. 1, ¶3), a scFV comprising the VL and VH regions from an anti-CD20 hybridoma (Leu-16) with a linker sequence inserted between the VL and VH regions (p. 1025, Col. 2, ¶5 to p.1026, Col. 1, ¶2), and human IgG1 hinge-Fc (p. 1026, Col. 1, ¶3 to Col. 2, ¶1); expression of the full length scFV-Fc in mammalian host cells as monomeric and multimeric forms (Figure 3); biologically active properties for each the scFv (Figure 5- competition cell-binding assay) and the Fc domains (Figure 6C-CDC lysis) in the expressed scFv-Fc protein; papain digestion of the scFv-Fc yielded predicted products of Fc and scFv with formation of non-covalent dimers, e.g., variable regions from scFv could interact with the corresponding variable regions on the other scFv subunit resulting in cross-paired structure or diabody" (p. 1029, Col. 1, ¶3; Figure 7).

Applicant is reminded that because the claim recites "comprising" language, the claim is not limited as to where or how the processing of the preproprotein into the mature polypeptide should occur, and is thus anticipated by Wu.

> A person shall be entitled to a patent unless-
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Jostock et al. (J. Immunological Methods 223:171-183 (1999); hereinafter referred to as "Jostock") as evidenced by Giri et al. (EMBO J. 13:2822-2830 (1994); hereinafter referred to as "Giri").

The interpretation of Claim 15 is discussed supra.

Jostock discloses Fc fusion proteins of IL-6 and hyper-IL-6 (H-IL-6, COOH-terminus of sIL-6 covalently fused to the NH2-terminus of mature IL-6 by flexible peptide linker) containing a thrombin cleavable site between the H-IL-6 and Fc portion (Figure 1A). Jostock discloses methods for expressing vector constructs in transfected COS-7 cells (Methods and Materials, section 2.5) comprising the following artificial polynucleotide sequence: a leader peptide (encoded by the pDC409 mammalian expression vector of Giri and as evidenced by Giri (Methods and Materials, p. 2829, Col. 2, ¶¶4 and 6), H-IL-6, cleavable propeptide (thrombin cleavage site), and IgG Fc (Methods and Materials, section 2.2). COS-7 cells expressed full-length chimeric protein (Figure 1B) that retained biological activity in vitro (Figure 3 cell proliferation and Figure 4 haptoglobin synthesis) and in vivo (Figure 5 haptoglobin synthesis). Thrombin treatment of the isolated H-IL-6Fc protein yielded biologically active H-IL-6 (Figure 6A).

Applicant is reminded that because the claim recites "comprising" language, a) artificial polynucleotides encoding any "peptide of interest" are encompassed within the scope and b) the claim is not limited as to where or how the processing of the preproprotein into the mature polypeptide should occur, and is thus anticipated by Jostock.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jostock et al. (J. Immunological Methods 223:171-183 (1999); hereinafter referred to as "Jostock") in view of Cabilly et al. (USPN 6,331,415; published December 18, 2001; filed June 10, 1988; hereinafter referred to as "Cabilly") and Sawai et al. (Am. J. Reproductive Immunol. 34:26-34 (July 1995); hereinafter referred to as "Sawai").

The interpretation of Claims 15-17 is discussed supra.

See the interpretation of Jostock as discussed supra. Jostock does not disclose an antibody heavy chain or light chain as the first and second peptides of interest, respectively, nor producing Fab fragments by the recombinant method.

Cabilly discloses in general methods of producing recombinant antibodies and Fab fragments using host cell cultures (col. 4, lines 53-63; Col. 5, lines 19-29); FIGS. 6 and 7 outline the construction of expression vectors for kappa and gamma anti-CEA chains respectively; vectors and methods suitable for use in host cells over a wide range of prokaryotic and eukaryotic organisms (Col. 8, line 41- Col. 10, line 25); construction of separate expression vectors for murine anti-CEA antibody heavy and light chains (Col. 16, line 29- Col. 24, line 19); transfection of E coli cells with the expression vectors and reconstitution of the heavy and light chain proteins into the full antibody (Col. 24, line 19- Col. 25, line 61); and preparation of Fab (Col. 27, line 41- Col. 28, line 28).

Sawai discloses a recombinant Fab fragment produced by cloning a truncated heavy chain gene (Fd) into one expression vector and the light chain gene into as second expression vector, transfecting mammalian cells, and secretion of the Fab fragment from the cells. Sawai teaches away from methods involving chemical proteolysis of IgG in vitro to generate Fab fragments because of reduced stability and yield.

It would have been prima facie obvious at the time of the invention to have produced the instant claimed method in view of Jostock, Cabilly and Sawai.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed method in view of Jostock, Cabilly and Sawai. Jostock discloses that monomeric forms of the peptides of interest, can be generated by introducing other specific protease cleavage sites into the chimeric molecule:

> "It can be anticipated that optimization of the thrombin cleavage reaction or the use of cleavage sites of other proteases will increase the efficiency of the cleavage process" and "The protease recognition site can be chosen after testing the fusion partner for susceptibility to a given protease. Therefore limited proteolysis via engineered protease cleavage sites appears to be a simple strategy to obtain soluble proteins..."(p. 181, Col. 1, ¶1 and 2).

Cabilly and Sawai disclose that recombinant antibody technology was well within one of ordinary skill in the art at the time of the invention and the reagents for performing this technology were readily available. Thus, engineering the heavy and light chain of an antibody according to Cabilly or the Fd region and light chain of an antibody according to Sawai into the construct of Jostock as the first and second peptides of interest, respectively, could have been accomplished using the techniques disclosed in the combined reference disclosures at the time of the invention. Still further, one skilled in the art would have been motivated to have produced a polynucleotide comprising the signal peptide, antibody fragment (e.g., heavy chain or Fd region), propeptide or cleavable linker, and antibody fragment (e.g., light chain) (or the reverse order of these antibody fragments) into a single, contiguous molecule for host cell expression and processing with defined proteolytic enzymes in order to specifically avoid non-specific proteolytic digestion of the recombinant antibody or Fab fragment using conventional methods (i.e., papain or pepsin digestion) and to increase the yield thereof. Thus the claims were prima facie obvious as the time of the invention in view of the combined reference disclosures.

16. Claims 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cabilly, Jostock and Sawai as applied to claims 15-17 above, and further in view of Inoue et al. (Applied microbiology and biotechnology 48(4): 487-492 (Oct. 1997); hereinafter referred to as "Inoue").

See the interpretation of Claims 15-17 as discussed supra.

See the interpretation of Cabilly, Jostock and Sawai as discussed supra.

Inoue discloses a method for producing a chimeric mouse-human Fab' using cDNAs encoding in the order the L chain, a flexbile peptide linker and Fd' fragment fused directly to the signal peptide encoding regions of the mwp gene for Bacillus brevis. Transformed cells produced Fab' protein in the culture medium.

It would have been prima facie obvious at the time of the invention to have produced the instant claimed method in view of Jostock, Cabilly, Sawai and Inoue. One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced the instant claimed method in view of Jostock, Cabilly, Sawai and Inoue. Inoue discloses the use of an artificial polynucleotide fusing the elements of a signal peptide, L chain, peptide linker and F'd region to produce a recombinant Fab fragment in a microbial host cell, and the method could readily have been combined with the reference disclosures of Jostock, Cabilly, Sawai to produce the instant claimed method for all the reasons set forth supra. Thus claims 15-17 would have been obvious at the time of the invention in view of Jostock, Cabilly and Sawai, and further in view of Inoue.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

LAB

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

Notice to Comply	**Application No.** 10/679,620	**Applicant(s)** REINL et al.	
	Examiner Lynn Bristol	**Art Unit** 1643	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
For CRF Submission Help, call (703) 308-4212 or 308-2923
PatentIn Software Program Support
Technical Assistance..703-287-0200
To Purchase PatentIn Software.........................703-306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR REPLY

Pursuant to 37 CFR 1.821, a sequence identifier must be provided for any amino acid sequences of four or more residues or nucleotide sequences of 10 or more nucleotides. The following omission has been identified in the specification:

p. 59, [¶220]- EQKLISEEDL

Applicants will need to provide a revised Sequence Listing, a computer readable form of the Sequence Listing and a statement. Please see the attached Notice to Comply Form, for which the Examiner has set a 3-month shortened statutory period for response.